Metabolism in vitro of the microtubule perturbers Ceratamine A and B

Disruption of microtubule dynamics results in anti-mitotic activity that can ultimately lead to cell death, especially in highly proliferative cells. This target has been of great interest in cancer drug discovery and was deemed successful with the approval of the effective anti-cancer agent Taxol®. Ceratamine A and B are natural products isolated from the marine sponge Pseudoceratina sp. They behave as microtubule perturbers, resulting in anti-mitotic activity with IC₅₀ values in the low micromolar range. Studies of in vitro metabolism were performed to begin to understand the pharmacokinetics of the ceratamines. Each compound was incubated within rat and human liver microsomes. Initial analysis was performed in a qualitative manner with LC-MS/MS techniques used for structure elucidation. Ceratamine A was converted to at least eight phase I metabolites by rat liver microsomes. The metabolites were the result of demethylations, at the secondary amine, tertiary amide, or methoxy groups, and aromatic hydroxylation. A similar metabolic profile was determined for ceratamine B, with five metabolites being formed by rat liver microsomes. Human liver microsomes, converted the parent drugs to four and three phase I metabolites, for ceratamine A and B, respectively. These metabolites were consistent with those already identified.